Structure of the human outer-mitochondrial membrane Monoamine Oxidase B at 1.7 Å resolution*

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Monoamine oxidase B (MAO B) is an outer-mitochondrial membrane-bound flavoenzyme that is a well-known target for anti-depressant and neuroprotective drugs [1]. The 3 Å resolution structure of recombinant human MAO B originally determined was of the enzyme complex with pargyline, an irreversible inhibitor covalently bound to the N5 atom of flavin coenzyme [2]. The crystal structure shows that the enzyme is dimeric. Each monomer binds to the membrane via a C-terminal transmembrane helix and by apolar loops located at various positions in the sequence. The helix of each monomer protrudes from the basal face of the dimer with each helical axis approximately parallel to the molecular two-fold axis. This observation suggests that the dimer binds to the membrane with its two-fold axis perpendicular to the membrane plane, and the C-terminal helices inserted in the lipid bilayer. Substrate binding to the enzyme involves negotiating a loop covering a 290 $Å^3$ entrance apolar cavity before reaching an apolar 420 $Å^3$ substrate cavity where the flavin coenzyme is located. The 1.7 Å isatin-MAO B structure allowed a detailed examination of the enzyme's active site [3,4]. A novel reversible MAO B inhibitor which is found as a contaminant in polystyrene plastics (1,4-diphenyl-2-butene) binds in both the entrance and substrate cavities. The new structures show that Ile199 functions as a "gate" whose side chain rotation allows for either separation or fusion of the two cavities. GRID analysis shows a hydrophilic region in the substrate cavity near the flavin that may facilitate the binding of the substrate amine moiety.

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1. Shih, J.C., Chen, K., Ridd & M.J. (1999) *Annu Rev Neurosci.* **22**, 197-217.
2. Binda, C., Newton-Vinson, P., Hubalek, F., Edmondson, D.E. & Mattevi, A. (2002) *Nat. Struct. Biol.* **9**, 22-26.
3. Binda, C., Li, M., Hubalek, F., Edmondson, D.E. & Mattevi, A. (2003) *Proc. Natl. Acad. Sci.*, **100**, 9750-9755.
4. Binda, C., Li, M., Hubálek, F.,., Herzig, Y., Sterling, J. Edmondson, D.E., Mattevi, A. (2003) Crystal structures of MAO B in complex with four inhibitors of the N-propargylaminoindan class. *J. Medicinal Chemistry*, **47**, 1767-1774

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